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LETTER TO THE EDITOR

Response to letter to the editor regarding “Efficacy of adding ramipril (VAsotop) to the combination of furosemide (Lasix) and pimobendan (VEtmedin) in dogs with mitral valve degeneration: The VALVE trial”

Dear editor,

We appreciate the interest in our VALVE trial by Dr Atkins and others. The authors open an important discussion and raise several interesting questions that we would like to address. However, we would like to point out that their letter to the editor appears to start with a misunderstanding. The aim or the primary hypothesis of the VALVE trial was not to address whether pimobendan “is all that is needed beyond loop diuretics to manage CHF in MMVD.” The only aim of the VALVE trial was to answer the question in dogs with MMVD that had reached the stage of congestive heart failure (CHF), ACVIM stage C or D, *if the addition of an angiotensin converting enzyme inhibitor (ACEI) to the basic treatment of a loop diuretic combined with pimobendan is superior to this basic treatment.* It is our opinion that this question has been considered clinically relevant by the veterinary community for quite some time.

Please allow us to further elaborate on the historical background of the ACEI issue and the underlying evidence. Approximately 30 years ago, ACEI found their way into veterinary cardiology and their use made pathophysiological sense. Subsequently, the IMPROVE,¹ LIVE,² and BENCH³ studies led to the approval of ACE inhibitors for dogs. These trials were groundbreaking in veterinary cardiovascular medicine, being large controlled clinical multicenter trials. However, it should be noted that they do not meet the CONSORT recommendations, which is mandatory for trials of this size conducted today.

At about the same time, the term “evidence-based medicine,” first mentioned in 1990 in human medicine,⁴ also found its way into the veterinary community, and was further defined in 2005.⁵ For many years, ACEI use in veterinary medicine was based on good evidence, the evidence being based on pathophysiological logic, experimental animals, extrapolation from human medicine, small veterinary studies, and expert opinion.

In fact, ACEI had been advised and used for many years to treat preclinical heart disease in dogs. However, subsequently it was shown that the systemic RAAS system was not measurably activated in MMVD, if furosemide was not part of the treatment.^{6,7}

This raised the question as to whether ACEI were beneficial in dogs with MMVD before the development of congestion and before the use of diuretics. Nevertheless, ACEI inhibitors continued to be widely used in dogs with preclinical MMVD (ACVIM stage B) for many years, and still are.

Then came the SVEP trial, a prospective randomized study which failed to show any benefit of enalapril in dogs with MMVD, when administered before the clinical occurrence of congestion.⁸ There was no measurable benefit demonstrated, neither in dogs with normal heart size (which today would be called ACVIM stage B1), nor in dogs with demonstrable compensatory left ventricular volume overload (which today would be classified as ACVIM stage B2). Despite this evidence, ACEI were still recommended in dogs with MMVD in the noncongested phase. Some arguments for ignoring the results of the SVEP trial were inadequate dosage and the inclusion of only one breed, the Cavalier King Charles Spaniel, which might not be representative of other breeds with the same disease. Next came a study similar to the SVEP trial, performed and published by Atkins et al.⁹ This trial had some different aspects from the SVEP trial, specifically multiple breeds were enrolled and a reasonable dosage of ACEI was chosen. This second prospective randomized trial did not show a statistical difference between dogs on an ACEI and those on placebo concerning the primary endpoint.⁹ In this publication, the authors carefully analyzed the data and offered plausible reasons to explain this unexpected result. One consideration was the possibility that starting ACEI treatment could be harmful to a certain subgroup of dogs with MMVD, and that if these dogs were excluded from the study, a benefit might be shown. One major problem with that argument is the fact that no known parameter could identify the proposed subgroup of dogs, at least at the present time to our knowledge.

Despite statistical nonsuperiority of ACEI over placebo in this second study, ACEI still are widely used in dogs with MMVD in ACVIM stages B1 and B2. In dogs with MMVD and decompensation (which today would be called ACVIM stage C), the usefulness of ACEI was not questioned, and they were still broadly recommended and used.

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Two studies subsequently were performed and published that evaluated an ACEI and pimobendan in dogs with MMVD, with treatment starting at the time of decompensation, based on objective evidence of pulmonary edema on radiographs.^{10,11} Both studies demonstrated the superiority of pimobendan over benazepril. However, a primary criticism of these studies was that they both lacked a treatment arm including both pimobendan plus an ACEI. Consequently, ACEI still are recommended and broadly used, based on expert opinion.^{12,13}

Now, after this historical review, let us explain the background of the VALVE trial. The VALVE trial was started very soon after the QUEST trial had ended.¹¹ The goal of the VALVE trial was to answer whether adding ACEI to furosemide plus pimobendan would improve outcome, and most VALVE coauthors had already been involved in the QUEST trial. To be consistent and credible, the authors largely adopted the QUEST trial's study protocol with some differences. In both the QUEST and the VALVE trials, the following features were identical: (a) dogs had to be in an advanced stage of MMVD with pulmonary edema objectively present on thoracic radiographs; (b) the study was not placebo-controlled, but the study authors were blinded to the treatment as the drugs were provided to the clients using a provider; (c) treatment failure was defined as decompensation despite the use of very high doses of furosemide. This dosage had been set at 12 mg/kg/d in the QUEST trial and at 15 mg/kg/d in the VALVE trial. Admittedly, these are very high dosages. Nevertheless, this was the definition of treatment failure in these respective studies. Please note, however, that the median maximal dose of furosemide in the VALVE trial was 9.1 mg/kg/d; we will further elaborate on the furosemide dose below.

In their letter to the editor, Atkins and colleagues point out the lack of additional treatments and comment that in the VALVE study we primarily increased the diuretic dose instead of adding various other drugs. However, we simply followed our protocol, which was similar to that of the QUEST trial. Changing and modifying the treatment options by adding different drugs might have led to unwanted effects of those drugs, either positive or negative, and ultimately might have influenced the answer to the primary question: "Does the addition of an ACEI improve the outcome of our patient population?"

Of course, a study always generates new questions, some of which were raised by Dr Atkins and colleagues in their letter to the editor. Was there an aldosterone breakthrough? Was the dose of the ACEI not high enough? Would the use of a mineralocorticoid receptor antagonist (MRA) be more beneficial?

Atkins et al. cite two studies that suggest an effect of spironolactone, but both studies were not performed with the currently recommended standard treatment using pimobendan. The only evidence, based on a published study, concerns the use of spironolactone.¹⁴ One of the cited studies had only a few dogs receiving pimobendan¹⁴ and this study's conclusions have been questioned.¹⁵ The second study, the Benazepril Spironolactone Study (BESST), is not yet published, but apparently these dogs also had not received pimobendan. Therefore, these studies also do not answer the

question of whether or not dogs that receive pimobendan and a diuretic will benefit from the use of an ACEI as well as an MRA.

Concerning the use of spironolactone in the VALVE trial, it is important to realize that the 13 dogs on spironolactone only referred to dogs prescribed spironolactone at the beginning of the study. In the course of the trial, 61 dogs eventually received spironolactone during progression of their disease (32 dogs in the dual therapy [DT] group and 29 dogs in the triple therapy [TT] group). However, we fully agree with Atkins and others that additional large-scale studies on this subject are necessary.

Concerning the starting dosage of furosemide in our VALVE trial, we agree that this dosage was quite high. However, it is common practice in some of our clinics to titrate the furosemide dosage down to the minimal effective dose as opposed to titrating the dosage up. The patients are discharged after stabilization in the clinic on similar diuretic dosages to prevent an immediate relapse of congestion, which might lead to owner disappointment and a potential decision for euthanasia. Once the dog has been stable for 3 days and the owners have learned to count the resting respiration rate (RRR), we start lowering the diuretic dose. The owners' RRR counts can be reviewed either by telephone or clinic visits to determine the minimal effective diuretic dose. In response to the concern raised by Atkins and colleagues, we have analyzed the furosemide dosages at the first and second recheck examinations. The mean furosemide dosage for both groups at day 7 was 5.91 mg/kg/d; DT, 5.89 mg/kg/d; TT, 5.91 mg/kg/d. After 1 month, the mean furosemide dosage was 5.32 mg/kg/d (DT, 4.78 mg/kg/d; TT, 5.80 mg/kg/d). These diuretic dosages were similar to those used in the QUEST study. The mean maximal furosemide dosage over the entire study period was 9.1 mg/kg/d.

Atkins and colleagues' next concern is the fact that RAAS suppression was not assessed using biomarkers, and that the ACEI dosage may have been inadequately low and was only doubled in 3 dogs. Actually, as reported in our paper, the mean dosage of ACEI was already 1.7 times higher than the dosage recommended by the manufacturer. Therefore, underdosing of the ACEI is an unlikely explanation of our results.

Atkins and colleagues mention "the known favorable effects of RAAS suppression on cardiac remodeling" supported by 2 citations. We respectfully disagree with this statement. First, as already discussed in this response, the study by Atkins et al as well as the SVEP trial, which both investigated a possible beneficial effect of ACEI in MMVD to postpone the occurrence of pulmonary edema, failed to prove this beneficial effect.^{8,9} Second, Atkins and colleagues cite a recent study that again was undertaken with the primary goal to show a beneficial effect of RAAS suppression to postpone the onset of pulmonary edema in dogs with MMVD.¹⁶ However, this study again failed to show this beneficial effect, and indeed there was not even a tendency toward a beneficial effect concerning the primary study goal. This last study did describe effects of RAAS suppression on N-terminal pro-brain natriuretic peptide (NT-proBNP) and cardiac size, but it did not just use an ACEI but the combination of an ACEI with an aldosterone antagonist.¹⁶

A further concern of Atkins and colleagues is the pretreatment with ACEI for several months before entering the VALVE trial. Returning to the important study by Atkins et al⁹: several dogs in the ACEI group died early in the study and it was argued that if these dogs had been excluded from the statistical analysis, ACEI would have been proven to have a positive effect on the course of the disease. If we adopt the same line of reasoning for our VALVE trial, we could conclude that these particular dogs, supposedly responding negatively to ACEI, never actually entered the VALVE trial because they would have been dead before they could have started the VALVE trial. Additionally, we tested preinclusion ACEI use in the multivariate analysis and found no effect. Furthermore, withdrawing the ACEI in the DT group might have disadvantaged dogs only in the DT group and not the TT group. We also tested the possible effect of center, because the number of dogs enrolled at the University of Munich (where the study was initiated) was significantly higher, compared with the other 3 centers. However, there was no significant difference in outcome among the study centers.

Finally, Atkins and others raised the question of owner compliance, which we can answer to be the same in both groups. Very importantly, no dog was lost because of renal compromise, or excluded from the study because of polyuria, polydipsia, or renal dysfunction.

We fully agree with Atkins and colleagues that our VALVE trial does not provide the final answer concerning RAAS suppression in dogs with MMVD and CHF. However, the VALVE trial is a large, prospective, randomized, multicenter study with a very high event rate that did not show any survival benefit with respect to the use of an ACEI in dogs with advanced MMVD. Therefore, given the data available today, we cannot in good faith recommend adding an ACEI to the basic treatment consisting of furosemide and pimobendan in dogs with MMVD in ACVIM stage C.

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